FDA prior to the Database Unblinding. FDA and the applicant discussed this change, specifically the concern by FDA that the expanded window may complicate the analysis of relapse and failure. FDA noted that it would be important to indicate how many patients did not come back for follow-up at the later visit (+21 to +28 days).

The majority of patients were evaluated for Test of Cure (TOC) during the +7 to +14 day window. The range was +6 days to +28 day. Only one patient had a TOC day beyond day +28 (#3300409, at day +38). There were 18 patients in the gatifloxacin group and 21 in the levofloxacin group whose TOC evaluation fell beyond the +7 to +14 day window. Fourteen patients, 7 from each treatment group, were seen in the +21 to +28 day window as the Test of Cure (#33 00409, #57 00738,#57 00157, #57 00773, #19 00117, #57 00542, #57 00540, #57 00832, #60 00817, #57 00745, #57 00836, #22 00369, #34 00130, #57 00602). All of these patients were considered cures. All of these patients were showing signs of improvement during study and had late follow-up clinically and radiographically. All CXRs either improved or resolved, and no further antibiotics were administered to these patients. It is acceptable to include these cases as cured in the analysis.

The sponsor supplied additional information regarding the patients who returned for the +21 to +28 day follow-up visit.

"One hundred eighty-four (184) of the clinically evaluable subjects were cured. Of these 129 had a Day +21 to +28 follow-up visit and 55 did not. Of these 55 subjects, 12 had NO late follow-up and 43 had a follow-up visit after day +14 but outside of the day +21 to +28 window."

FDA review of this data revealed that 22 patients did not have late follow-up after Day +14 (1300192 A,2500489 B, 2800041 A, 3700434 B, 3700529 B, 4900393 B, 5500323 A, 5700156 A, 5700159 A, 5700426 A, 5700429 A, 5700583 A, 5700601 A, 5700721 A, 5700742 A, 5700744 B, 5700770 A, 5700772 A,5700775 B, 5700780 A,5700826 B, 6000070 A; A= Levofloxacin, B = Gatifloxacin.) Fifteen were in the levofloxacin group and 7 were in the gatifloxacin group. If these were counted as Relapses, the overall number of relapses would be 9% 16/178) in the levofloxacin group and 5 % (8/172) in the gatifloxacin group. These are small numbers and the rates are similar between groups. When an overall success/failure outcome is calculated included failures and relapses the comparative outcomes between the groups remains unchanged. (please see statistical review for additional details)

8.1.3.1.6 OUTCOME EVALUATION:

Clinical Evaluation:

Each patient was assigned a clinical response of Cured, Failure or Unable to Determine.

Medical Officer Comment: FDA reviewed each of these assignments for outcome. The results of each review are listed in a Medical Officer Comment following the protocol definition for each outcome.

CURED:

- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and chest x-ray abnormalities were improved or had not progressed; OR
- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and no during or post-treatment chest x-ray was performed (These patients were not included in the evaluable subset).

Medical Officer Comment: *For all of the "cured" patients who were considered evaluable, signs and symptoms were reviewed via JMP data base for the Test of Cure Day. For the majority of patients that day was within 7-14 days after the end of therapy. The following distribution was seen in symptom response:*

FDA Evaluation of Cured by Clinical Status of Signs and Symptoms

Symptom Response	*Number of Symptoms*	*Number of Symptoms Related to CAP*	*Number of Cured Patients with CAP Symptoms*
Resolved	*2888*	*1455*	*314*
Improved	*851*	*310*	*158*
Same	*115*	*7*	*6*
Worse	*38*	*4*	*4*
Unknown	*456*	*3*	*3*
New	*19*	*3*	*3*

**note that the patient category is not mutually exclusive as the patients had two or more signs and symptoms evaluated.*

For the majority of symptoms recorded, the outcome evaluation was Resolved. Further review of the total symptom base revealed a subset of symptoms that defined CAP. The total number of patients with one or more CAP symptom reported to have resolved was 158 or 45% of the clinically evaluable population. These symptoms were evenly divided between the treatment groups for the resolved category (levofloxacin group 51%, gatifloxacin group 48%). More patients were reporting improved symptoms in the levofloxacin than the gatifloxacin group (61% vs 39%).

As per the definition of cure, all signs and symptoms were to have resolved or improved to such a level that no further antibiotics were needed. As noted in the table, several patients had CAP symptoms that remained the same, worsened, or were of unknown resolution. Because the TOC cure window was widened to include the follow-up visit at -21 to +28 days, CRF review of patients having a respiratory symptom which was designated as same, worse, unknown or new was performed. Four patients had CAP symptoms listed as worsening, two in each treatment group. Each patient had only one CAP symptom that was designated as having worsened. All had clearing of CXR at the final visit and none went on to relapse. All of the other symptoms related to CAP were either resolved or improved. Of those with same, unknown or new symptoms, none of them went on to relapse. Again only one symptom was noted for each patient, and many were headache or malaise. Review of the CRFs by the FDA reviewer agrees in general with counting these as cures.

Regarding the issue of Cure representing strictly the Resolved signs and symptoms verses resolved and improved, the original study design allowed for evaluation of patients at the +7 to +14 day window and again at the +21 to +28 day window. This would allow any patient with improved symptoms the opportunity to further resolve or continue to worsen, thus representing a relapse. When the applicant widened the window this made the definition of cure more difficult. As it turned out, most of the patients reported symptoms that resolved and most of the evaluation days were in the earlier window. Therefore, upon review of patients who had symptoms that improved as opposed to resolved, further investigation was undertaken, via CRF to ensure that these patients did not relapse at a later date. Two of the patients listed with improved symptoms at TOC date went on to become a relapses (# 39-220, #57-577). Each patient was found to relapse in the +21-28 day window.

Finally, the assignment of cure used by the applicant was the one assigned by the applicant and not necessarily that checked off by the clinician at the time of final evaluation. There were only a small number of discrepancies between these assignments. FDA review of these changes was in agreement with the applicant's review. This was mostly due to additional data which was available at the time of the applicant's review. Most of the outcomes that were discrepant occurred because the investigator had checked off unable to determine for the clinical outcome. The applicant reassigned these to cure or failure (Cure: 8 patients for Gatifloxacin, 9 patients for Levofloxacin; Failure: 6 patients for Gatifloxacin; 5 patients for Levofloxacin). Failure assignment was due to patient receiving additional antibiotics. FDA review of these cases is in agreement with the applicant.

FAILURE:

One or more of the following:

- Signs and symptoms relevant to the original infection persisted or progressed after at least 3 days of therapy;
- New pulmonary or extrapulmonary clinical findings consistent with pneumonia developed;
- Radiographic abnormalities progressed;
- Additional antimicrobial therapy was needed for treatment of the pneumonia under study;
- Patient died and death was due to pneumonia.

All treatment failures were due to worsening or persistence of signs and symptoms, 18 in the gatifloxacin arm and 12 in the levofloxacin arm. None of the pre-treatment pathogens displayed resistance to either study drug, nor were any post-treatment pathogens identified. Further, none of the treatment failures had documented persistence of a pre-treatment pathogen. Most treatment failures received post-treatment antibiotics.

Reason Clinical Response is Failure, Clinically Evaluable Patients Protocol AI420-038

	Number of Patients (%)					
Frequency/Reason	Gatifloxacin N = 172		Levofloxacin N = 178		Total N = 350	
Number of Failures	18	(10)	12	(7)	30	(9)
Persistence or Worsening of Signs/Symptoms	18	(100)	12	(100)	30	(100)

(Reference vol 6, p100)

Medical Officer Comment: Review of the above cases CRF and JMP database by the FDA is in agreement with the applicant's assignment of failure.

UNABLE TO DETERMINE:

Clinical response was termed Unable to Determine (UTD) when a post-treatment evaluation of clinical signs and symptoms was not obtained, or when another systemic antibiotic with documented activity against the isolated pathogen(s) for an infection other than pneumonia, was administered prior to evaluation.

Reason Clinical Response is Unable to Determine, Clinically Eligible Patients Protocol AI420-038

	Number of Patients		
Reason	Gatifloxacin N = 203	Levofloxacin N = 197	Total N = 400
Number of Responses Unable to Determine	17	10	27
Inadequate Follow-up	5	7	12
Discontinuation due to AE or SAE	7	1	8
Other Reason	4	-	4
Other Systemic Antibiotic Given for an Infection Other Than Pneumonia	1	2	3

(Reference: Vol 6., p. 114)

The "other" reasons in the gatifloxacin group include termination of therapy for suspected endocarditis, withdrawal of consent, death and self-administration of antibiotics.

Medical Officer Comment: FDA review of SAS files and CRFs verified the above table. Patients from the above table with adverse events received generally less than 5 doses of medication and were withdrawn from the study. The number of patients ranked as unable to determine is similar between the two treatment groups. Slightly more patients in the gatifloxacin group were considered to have discontinued due to an adverse event or serious adverse event; however, these cases represent only those who were classified

as having a response of "unable to determine" (please refer to adverse event section below for further discussion). Calculation of the efficacy rates would include these patients in the denominator for the rate calculation in the Clinically Eligible analysis and these patients would be excluded from the Clinically Evaluable analysis.

8.1.2.1.7 MICROBIOLOGICAL EVALUATION:

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine according to definitions in the protocol. Typical bacterial pathogens such as *S. pneumoniae*, were microbiologically evaluable for response only if susceptible to both study drugs. Atypical bacterial pathogens, regardless of diagnostic method, were microbiologically evaluable for response.

Medical Officer Comment:
Microbiological Response was based upon clinical response of the patient who had a documented pretreatment pathogen. Thus, the clinical response categories of Cure, is a clinical one, but when used in the expression Bacteriologic Eradication may connote the impression that the pathogen was demonstrated to be microbiologically eradicated. This leads to confusion when expressing the result for serologically diagnosed atypical pathogens, especially where the documentation of a single high titer made the diagnosis. Therefore, this reviewer recommends the results be discussed as a clinical response based upon a microbiologic diagnosis at entry.

The impact of this syntax will be discussed in the analysis section, and will include critique of the shorthand expression "Bacteriologic" eradication rate, where, especially for the atypical pathogens it is very misleading.

8.1.3.1.8 STATISTICAL METHODS:

Data Sets -- There were four groups of interest:

- All Treated Patients: All patients who received at least one dose of study drug.
- Clinically Eligible Patients: All Treated Patients with a diagnosis of community-acquired pneumonia at entry.
- Clinically Evaluable Patients: All Clinically Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment (Test of Cure) assessment in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells).

Efficacy Analyses – The primary efficacy assessment was the clinical response taken at the Test of Cure Visit in the Clinically Evaluable group. Ninety-five percent confidence intervals for the difference in response rates were constructed using an exact method. Intervals were also constructed for the clinical response taken at the Test of Cure Visit in

Clinically Eligible Patients and in All Treated Patients. Additional secondary efficacy analyses included clinical cure rates by prognostic factors and by severity of pneumonia for Clinically Evaluable Patients as well as cure rates and eradication rate by pathogen for Microbiologically Evaluable Patients.

Based on an estimated 80% clinical cure rate for patients with community-acquired pneumonia treated with levofloxacin, 150 evaluable patients per arm would yield a 90% power to claim the cure rate for gatifloxacin is at most 15% less than the rate for levofloxacin (α= 0.05, two-sided). Assuming an 80% evaluability rate, the necessary sample size was calculated to be 376 patients, 188 patients per treatment arm. However, enrollment was allowed to progress until the end of the respiratory infection season in order to obtain maximum efficacy data concerning respiratory pathogens (total enrollment 418 patients).

Medical Officer Comment: The decision to extend enrollment was made with a blinded database. This is acceptable to FDA.

Safety Analyses – All patients who received at least one dose of study drug were evaluated for safety. All safety data were summarized with descriptive statistics and tabulated.

8.1.3.2 EFFICACY RESULTS:

8.1.3.2.1 Clinical Efficacy:

Of the 417 patients treated (209 gatifloxacin; 208 levofloxacin), 88% received PO therapy only, 11% received IV therapy followed by PO, and 1% received IV therapy only. The median duration of therapy regardless of the route of administration was 12 days in the gatifloxacin group and 14 days in the levofloxacin group.

Clinical Response in Evaluable Patients - Ninety percent (154/172) of gatifloxacin patients and 93% (166/178) of levofloxacin patients had a clinical response of cured (95% CI = -11.5%, 3.6%). All failures were due to the persistence or worsening of pre-treatment signs and symptoms. The clinical cure rate was not markedly affected by prognostic factors in either treatment arm. There was one relapse in each treatment arm. New infections were reported in 10 gatifloxacin patients and 14 levofloxacin patients, most commonly involving the upper respiratory tract.

Clinical Response in Eligible Patients - Eighty-three percent (168/203) of gatifloxacin patients and 89% (175/197) of levofloxacin patients were considered clinical cures (95% CI = -14.5%, 1.7%). A total of 27 (7%) patients were evaluated as unable to determine [17 (8%) gatifloxacin, 10 (5%) levofloxacin]. The most common reason in the gatifloxacin group was premature discontinuation due to an adverse event, and in the levofloxacin group it was inadequate follow-up.

Applicant Clinical Efficacy Analysis

Subgroup	Gatifloxacin	Levofloxacin	95% Confidence Interval*
All Treated Patients	83% (173/209)	88% (183/208)	-13.1%, 2.7%
Eligible Patients	89% (168/203)	95% (175/197)	-14.5%, 1.7%
Evaluable Patients	90% (154/172)	93% (166/178)	-11.5%, 3.6%

(Reference. Vol 6) * CI of the difference in cure rates.

Medical Officer Comment: In general the FDA was able to verify the applicant's analysis as described above. However, additional sensitivity analyses were performed by the FDA. One of the most conservative analysis counted the missing data as failures in the gatifloxacin group and successes in the levofloxacin group. The 95% confidence intervals of the difference were somewhat wider with this analysis (-17.9%, -3.2%). The results of this conservative analysis would indicate that the results are not robust enough for this type of analysis. A more clinically interesting analysis is that of global failure, where patients who failed at the "test of cure" visit or relapsed or had a new respiratory tract infection were counted as failures. The 95% confidence interval for this analysis in the evaluable subset was –9.5%, 4.8%.

Another consideration in the analysis of efficacy in this clinical trial is the fact that patients were stratified by initial route of administration of study drug, either IV or PO. A relatively small percentage of patients were given IV therapy (12%). There is a small treatment difference for the patients on oral therapy only (85% for gatifloxacin, 88% for levofloxacin, 95% CI –9.5%, 2.2%, in evaluable patients). The cure rate for patients receiving IV therapy was lower in the gatifloxacin group than that for the levofloxacin group, though the numbers were relatively small. If one assumes this may be a surrogate for severity, this hypothesis is not borne out when one looks at the outcome rates based on physician assessed severity scoring. Patients on gatifloxacin who were considered to have severe pneumonia had a 91% (63/69) cure rate compared to a levofloxacin cure rate of 90% (53/59).

The above analyses support the efficacy of gatifloxacin for the treatment of community acquired pneumonia.

8.1.3.2.2 MICROBIOLOGICAL EFFICACY:

Clinical Outcome for Microbiologically Documented Infections:
In both treatment arms, polymicrobal infection was documented in approximately one-third of patients with pre-treatment pathogens. Only two pretreatment isolates were not sensitive to gatifloxacin and levofloxacin. One isolate, *Pseudomonas sp.* was resistant to both (considered a clinical cure), and the other was an isolate of *S. epidermidis* resistant to levofloxacin only (this patient was not considered to be eligible due to a negative CXR.

The overall bacteriologic eradication rate in the Microbiologically Evaluable group was 91% (121/133) in the gatifloxacin arm and 94% (105/112) in the levofloxacin arm. Persistence in the gatifloxacin group was presumed only, whereas one case of *S. pneumoniae* persistence was microbiologically documented in the levofloxacin group. All

(54) isolates of *H. influenzae*, *M. catarrhalis*, *K. pneumoniae* and *L. pneumophila* were eradicated. Eradication of *S. pneumoniae* in the gatifloxacin group was 86% (12/14) and 81% in the levofloxacin group (13/16). Eradication of *S. aureus* in the gatifloxacin group was 92% (22/24) and 86% (12/14) in the levofloxacin group. Eradication of *C. pneumoniae* and *M. pneumoniae* was 100% (8/8) and 94% (15/16) in the gatifloxacin group, respectively. Eradication of *C. pneumoniae* and *M. pneumoniae* was 83% (10/12) and 100% (13/13) in the levofloxacin group, respectively.

The clinical cure rate by pathogen in Microbiologically Evaluable Patients was similar in the two treatment groups (gatifloxacin 91%; levofloxacin 95%). Both gatifloxacin and levofloxacin had excellent activity against the most common typical pathogens and atypical pathogens. The clinical cure rates for *H. influenzae*, *M. catarrhalis*, *K. pneumoniae* and *L. pneumophila* were all 100%. The clinical cure rate for *S. pneumoniae* was 87%. Notably, there were two cases of *S. pneumoniae* bacteremia in the microbiologically evaluable subset, both in the gatifloxacin group; one was a clinical cure (026-550), and the other was a clinical failure (009-114).

The clinical cure rate for atypical pathogens was excellent in both treatment arms, 29/30 (97%) for gatifloxacin and 27/29 (93%) for levofloxacin.

Clinical Cure Rate by Pathogen, Microbiologically Evaluable Patients Protocol AI420-038

Pathogen[a]/Subtype	Number Cured/Number Isolated or Documented (%) Gatifloxacin N = 92		Levofloxacin N = 81		Total N = 173	
H. influenzae	9/9	(100)	12/12	(100)	21/21	(100)
β-Lactamase +	3/3	(100)	5/5	(100)	8/8	(100)
β-Lactamase -	6/6	(100)	7/7	(100)	13/13	(100)
S. pneumoniae	12/14	(86)	14/16	(88)	26/30	(87)
Penicillin Susceptible	7/8	(88)	10/11	(91)	17/19	(89)
Penicillin Intermediate	5/6	(83)	3/4	(75)	8/10	(80)
Penicillin Testing Not Done	-		1/1	(100)	1/1	(100)
M. catarrhalis	11/11	(100)	8/8	(100)	19/19	(100)
β-Lactamase +	10/10	(100)	7/7	(100)	17/17	(100)
β-Lactamase -	1/1	(100)	1/1	(100)	2/2	(100)
K. pneumoniae	2/2	(100)	2/2	(100)	4/4	(100)
H. parainfluenzae	25/27	(93)	13/13	(100)	38/40	(95)
β-Lactamase +	4/4	(100)	4/4	(100)	8/8	(100)
β-Lactamase -	18/20	(90)	9/9	(100)	27/29	(93)
β-Lactamase Testing Not Done	3/3	(100)	-		3/3	(100)
S. milleri	2/3	(67)	6/6	(100)	8/9	(89)
S. aureus	22/24	(92)	12/14	(86)	34/38	(89)
β-Lactamase +	-		1/1	(100)	1/1	(100)
Methicillin Sensitive	22/24	(92)	11/13	(85)	33/37	(89)
Other Gram-positives[b]	5/6	(83)	7/7	(100)	12/13	(92)
Other Gram-negatives[c]	4/7	(57)	5/5	(100)	9/12	(75)
M. pneumoniae	15/16	(94)	13/13	(100)	28/29	(97)
L. pneumophila	6/6	(100)	4/4	(100)	10/10	(100)
C. pneumoniae	8/8	(100)	10/12	(83)	18/20	(90)
TOTAL	121/133	(91)	106/112	(95)	227/245	(93)

[a] A patient may have more than one pathogen isolated pre-treatment.

[b] Gram-positive pathogens isolated from <5 patients included [(x/y) = (gatifloxacin/levofloxacin)]: *S. pyogenes* (1/2), *S. canis* (2/0), *S. agalactiae* (1/0), *S. sanguis* (0/2), *S. epidermidis* (2/2), *S. warneri* (0/1).

[c] Gram-negative pathogens isolated from <5 patients included [(x/y) = (gatifloxacin/levofloxacin)]: *P. aeruginosa* (3/1), *C. freundii* (0/1), *C. diversus* (1/0), *K. oxytoca* (0/1), *K. ornithinolytica* (1/0), *E. cloacae* (0/1), *S. marcescens* (0/1), *Haemophilus sp.* (1/0), *A. faecalis* (1/0).

(Reference vol 6, p. 108)

Medical Officer Comment:

FDA review of the database provided by the applicant is in agreement. It should be noted that patients may have more than one pathogen documented at baseline and the

above table applies clinical outcomes to each pathogen without deciding on which may be the putative agent causing the CAP.

In addition this outcome measure subsets the clinically evaluable patients into a group having a microbiologic diagnosis (culture or serology) at baseline, with CURE being defined clinically. Thus, the oddity of stating that the Atypical Pathogens were eradicated in a microbiologically evaluable patient. Further analyses should be applied to some of these pathogens (see discussion of atypical pathogens below).

For S. pneumoniae, H. influenzae, M. catarrhalis, H. influenzae, and S. aureus, there are adequate numbers of cases treated in this study to support the efficacy of gatifloxacin in the treatment of community acquired pneumonia due to these pathogens. There are insufficient numbers of cases of K. pneumoniae to evaluate the efficacy of gatifloxacin for this pathogen.

No Penicillin-resistant S. pneumoniae isolates in the baseline sputum cultures were documented in microbiologically evaluable group in study -038.

Bacteriologic Responses in Microbiologically Documented Infections:
The bacteriologic eradication rate was similar in the two treatment groups (91% gatifloxacin; 94% levofloxacin). Eradication of the most common respiratory pathogens was excellent in both treatment groups. All isolates of *H. influenzae*, *M. catarrhalis*, *K. pneumoniae*, and *L. pneumophila* (54) were eradicated or presumed eradicated in both treatment arms. *S. pneumoniae* was eradicated in 86% of gatifloxacin patients and 81% of levofloxacin patients.

Medical Officer Comment:
It is of interest to note that the eradication rate which is quoted above by the applicant is comprised of patients with documented eradication (positive culture followed by a negative culture, in the case of culture proven cases) or presumed eradicated (microbiologically evaluable without a follow-up culture). The majority of these "eradicated" responses were presumed eradication. The classes of response were relatively similar between treatment arms. It is important to understand the use of the terms bacteriologic cure rates, and that in this model it does not have the same stringency that it would in an animal model where confirmation of bacteriologic cure would have a much higher proportion of follow-up culturing.

Bacteriologic Response Classification for Microbiologically Evaluable Isolates

	Gatifloxacin	Levofloxacin	Total
Eradicated	3	8	11
Presumed eradication	118	97	215
Persisted	0	1	1
Presumed Persisted	14	6	20
TOTAL	135	112	247

Based on SAS transport file analysis.

In addition, the atypical pneumonias that were documented were documented by serology for the most part. It is misleading to state that "All of the ..... L. pneumophila and C. pneumonia isolates were eradicated". Only M.pneumoniaes were reported by culture, and only eight All Treated Patients diagnosed with M. pneumonia had it documented by culture. For further evaluation of the atypicals please see below.

8.1.3.2.2.1 NEW INFECTIONS: Twenty-four patients had new infections, ten in the gatifloxacin group and.14 in the levofloxacin group. No cultures were performed.

The most common new infections were URIs (upper-respiratory tract infections) and sinusitis. Nearly all new infections occurred greater than one week post-treatment.

New Infections, Clinically Evaluable Patients
Protocol AI420-038

Infection Type/Diagnosis	Number of Patients (%) Gatifloxacin N = 172		Levofloxacin N = 178		Total N = 350	
Number of Patients Reporting Any New Infection[a]	10	(6)	14	(8)	24	(7)
URI	3	(2)	3	(2)	6	(2)
Sinusitis	2	(1)	4	(2)	6	(2)
Bronchitis	3	(2)	-		3	(1)
LRI	1	(<1)	-		1	(<1)
Otitis Media	-		2	(1)	2	(<1)
Conjunctivitis	-		2	(1)	2	(<1)
Vaginitis	1	(1)	1	(1)	2	(<1)
Tooth Abscess	-		1	(1)	1	(<1)
Thrush	-		1	(1)	1	(<1)
UTI	1	(1)	-		1	(<1)
Vomiting	-		1	(1)	1	(<1)

[a] Patients may have more than one new infection.

(Reference vol 6, p. 112)

Medical Officer Comment: Of interest are the 10 patients diagnosed with new respiratory tract infections, including bronchitis, pneumonia, and upper respiratory tract infection. Review of these CRFs revealed 6 patients who were considered to have failed therapy due to the need for additional antibiotics. The patient noted to have pneumonia in the Levofloxacin group was considered a cure. This patient had improvement or resolution of the pneumonia documented in November and during the following January the patient was noted to have a new infection. This was not considered a relapse. It would have been approximately 60 days after the TOC date, well beyond the follow-up

window. FDA agrees that this should be considered a new occurrence of pneumonia. The remaining patients had no evidence of progression of pneumonia.

8.1.3.2.2.2 RELAPSES:

One patient from each treatment arm relapsed. In the gatifloxacin group relapse occurred in a 45 year-old female who had multilobar disease but no pre-treatment pathogens isolated (057-577). All signs and symptoms resolved or improved after 14 days of oral therapy but the patient developed "asthmatic bronchitis" by Day +19, which was characterized by a recurrence of pre-treatment signs and symptoms. She was treated with doxycycline and gentamicin on Day +23.

In the levofloxacin group, relapse occurred in an 86 year-old female who had no pre-treatment pathogen isolated (039-220). Initially her signs and symptoms improved with 11 days of therapy. However, by Day +24 her signs and symptoms had returned and her physician indicated she had a new infection of pneumonia, which was treated with cefpodoxime.

Relapse Rate Among Clinically Cured Patients,
Clinically Evaluable Patients
Protocol AI420-038

	Number of Patients (%)					
	Gatifloxacin N = 172		Levofloxacin N = 178		Total N = 350	
Clinical Cures	154	(90)	166	(93)	320	(91)
Number of Patients Reporting Relapse of Pneumonia	1	(1)	1	(1)	2	(1)

(Reference vol 6, p.111)

Medical Officer Comment: Review of CRFs and JMP data set are in agreement with applicant's analysis of relapse. The issue of missing data and its impact on this endpoint has been discussed previously in this review.

8.1.3.2.2.3 RESISTANCE ISSUES:

All but two of the pre-treatment isolates were sensitive to gatifloxacin and levofloxacin. One exception was an untyped sputum isolate of *Pseudomonas* which was resistant to gatifloxacin and levofloxacin (060-071). The other was a blood isolate of *S. epidermidis* which had intermediate susceptibility to levofloxacin, but was susceptible to gatifloxacin (007-597).

Medical Officer Comment: The clinical outcome of these patients was unable to determine according to protocol definitions.

8.1.3.2.2.4 ATYPICAL PNEUMONIA:

Sixty-seven atypical pathogens were identified. 34 in the gatifloxacin arm and 31 in the levofloxacin arm. Thirty-eight patients had infection with an atypical pathogen and no typical pathogens, 21 in the gatifloxacin arm and 17 in the levofloxacin. Patients had a

single atypical pathogen, except in two instances in the levofloxacin arm; patients 025-493 and 035-331 both had evidence of co-infection with *M. pneumoniae* and *L. pneumophila*. The former also had pre-treatment sputum cultures positive for *S. pneumoniae*.

All Treated Patients
Protocol AI420-038

	Number of Patients (%)	
	Gatifloxacin	Levofloxacin
Number of Patients with Atypical Pathogen	34	31
Single Atypical Pathogen Only	21	17
M. pneumoniae	11	8
C. pneumoniae	5	8
L. pneumophila	5	1
Multiple Atypical Pathogens Only	-	1
M. pneumoniae + *L. pneumophila*	-	1
Atypical and Typical Pathogens	13	13
M. pneumoniae + typical pathogen(s)	6	7
C. pneumoniae + typical pathogen(s)	6	4
L. pneumophila + typical pathogen(s)	1	1
M. pneumoniae + *L. pneumophila* + typical pathogen	-	1

(Reference vol6, p 81)

The diagnosis of infection with an atypical pathogen was made by serology only in 82% of cases.

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Diagnosis of Atypical Pathogens, All Treated Patients
Protocol AI420-038

	Number of Pathogens From Patients Receiving Gatifloxacin/Levofloxacin		
	M. pneumoniae	*L. pneumophila*	*C. pneumoniae*
Total Number of Atypical Pathogens[a]	17/17	6/4	11/12
Method of Diagnosis			
Serology Only	13/13	5/4	9/11
PCR Only	-	-	1/0
Serology & PCR	0/1	-	1/1
Serology & Culture	0/1	-	-
PCR & Culture	2/1	-	-
Serology & PCR & Culture	2/1	-	-
Urinary Antigen	-	1/0	-

[a] A patient may have more than one atypical pathogen-isolated pre-treatment.
(Reference: Vol. 6, p. 83)

Medical Officer Comment: In an FDA analysis similar to that of the applicant, the overall rate of an atypical as a sole pathogen was similar (both rates = 58%). None of the patients identified with atypical pneumonia had cross-reactive serology. Combinations of atypical and "typical" pathogens were seen in roughly half of the cases reported. (see table below).

Microbiologically Evaluable Patients who met the Serologic Criteria for Atypical Pneumonia Pathogen

	M.pneumoniae (N=29)	*C.pneumoniae (N=20)*	*L.pneumophila (N=10)*	*TOTAL*
Sole pathogen	*18 (62%)*	*11 (55%)*	*5 (50%)*	*34/59 (58%)*
Atypical + M. pneumoniae	*NA*	*0*	*2*	
Atypical+ C. pneumoniae	*0*	*NA*	*0*	
Atypical+ L. pneumophila	*2*	*0*	*NA*	
Atypical + typical path	*10 (35%)*	*9 (45%)*	*4 (40%)*	
Note: only Atyp+Atyp	*2*	*0*	*2*	

The FDA recommended that the applicant attempt to culture these pathogens as well as diagnose them by serologic methodologies. Only 7 M. pneumoniae were isolated by culture, three in the levofloxacin group and four in the gatifloxacin group. All of the culture documented cases were designated at clinical cures. (see appendix).

M. Pneumoniae Infections:

Review of M. pneumoniae pathogens reveals 35% (10/29) of the patients had another "typical" pathogen isolated in culture. Serologic methodology which was used included PCR, and IgG / IgM by IFA (indirect fluorescent antibody). Criteria for diagnosis by the applicant per protocol were as follows:

Mycoplasma pneumoniae case definition (one or more of the following):

- A single IgM indirect fluorescent antibody (IFA) titer of ≥1:16 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of ≥1:32 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit description reveals the following discrepancies:

From the Zeus test kit insert for **IgM** provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:16 screening dilution: Equivocal Results. Retest at a later date to evaluate the possibility of a seroconversion.
- Florescence intensity of greater than 1+ at 1:32 or higher: ACTIVE or CURRENT INFECTION with M. pneumoniae."

The applicant should have made a distinction between a single high titer which, according to the label should have been ≥ 1:32, and repeat titers with a four-fold rise beginning at 1:16. Of the microbiologically evaluable patients designated as M. pneumonia infections, most had baseline values on of ≤ 1:16. One case was diagnosed solely based upon the fact that the initial titer was 1:32 with repeat of < 1:16. Another based on baseline titer of 1:16 with follow-up not being done. These two cases may represent false positive cases.

From the Zeus test kit insert for **IgG** provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:32 screening dilution but not more than 1:64: Equivocal Results. PRESENT OR PAST INFECTION with M. pneumoniae.
- Florescence intensity of greater than 1+ at 1:64 or higher: RECENT or PAST INFECTION with M. pneumoniae.

* It is recommended that in the event of borderline interpretations further testing be performed to evaluate the possibility of a later seroconversion."

The applicant should have used the criterion of greater than 1:32 rather than ≥ 1:32. Eleven of the infections diagnosed as M. pneumonia were based solely upon a titer equal to 1:32. Some of these infections may not represent acute infection if the latter criterion were applied.

PCR testing is experimental at this time. However, it had good correlation with the M. pneumoniae cultures. Six of the seven patients with culture positive M. pneumoniae had positive PCR tests.

Overall, the number of infections due to M. pneumoniae may be somewhat less than the applicant states, given the above analysis. In addition, if patients with "typical" pathogens also isolated from sputum are eliminated from the list, the number becomes smaller. Only one patient was not clinically cured (Gatifloxacin group). In general, each study drug may be highly efficient in treating this pathogen, OR as the majority of cases of M. pneumonia resolve without treatment it may be difficult to attribute the exact clinical response rate in this circumstance.

Regarding the Bacteriologic response of M. pneumonia, 7 microbiologically evaluable patients had initial isolate from positive culture. Follow-up information on these isolates was not provided by the applicant. Therefore, the only response could be presumed eradicated based upon clinical cure. Because the diagnosis for the majority was made on a serologic basis, it would be inaccurate to describe the pathogen as being eradicated. However, based upon the definition in the protocol one could designate them as being presumed eradicated.

C. pneumoniae:

Review of C. pneumoniae infections reveals that 45% (9/20) of patients had another typical pathogen isolated in culture. Serologic methodology which was used included PCR, IgM and IgG by IFA. Criteria for diagnosis by the applicant per protocol was as follows:

Chlamydia pneumoniae case definition (one or more of the following):

- A single IgM indirect fluorescent antibody (IFA) titer of ≥1:10 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of ≥1:512 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit insert reveals the following discrepancies:

From the MRL Diagnositics' test kit description for **IgM** provided by the applicant the interpretation/significance is a follows:

- "IgM endpoint titers of 1:20 and greater are considered presumptive evidence of infection.
- IgM endpoint titers less than 1:20 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels."

The applicant should have utilized the level of ≥ 1:20 and not ≥ 1:10 according to the package insert. All but one patient designated as having C. pneumoniae had IgM titers of <10 which did not change upon subsequent testing. None of the diagnoses were made soley on the basis of this titer.

From the MRL Diagnostics' test kit discription for **IgG** provided by the applicant the interpretation/significance is as follows:
"For C. pneumoniae:
IgG endpoint titers of ≥ 1:512 and greater are considered presumptive evidence of current infection.

- A single specimen endpoint titer ≥ 1:64 and < 1:512 should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. IF the second specimen exhibits a titer ≥ 1:512 or a four fold increase over that of the initial specimen, current (acute) infection is indicated.
- Unchanging titers ≥ 1:64 and < 1:512 suggest past infection.
- IgG endpoint titers less than 1:64 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. "

The applicant applied the test kit criteria correctly for the IgG.

PCR testing is experimental at this time. Three of the patients had positive PCR results for C. pneumoniae. There were no C. pneumoniae isolated by culture.

Overall the number of infections with C. pneumoniae was based solely upon serologic diagnosis. Two patients were designated as clinical failures, both in the levofloxacin group. One patient had other pathogens isolated in the sputum. Gatifloxacin appears to be equally efficacious in treating C. pneumoniae as clarithromycin.

Five patients in the levofloxacin and four patients in the gatifloxacin group had a "typical" pathogen diagnosed in the sputum as well.

Regarding Bacteriologic response for C. pneumoniae, no cultures were positive for this organism, hence the outcome is based upon the clinical outcome and would be classified as presumed eradicated. It would be inaccurate to describe a bacteriologic response for this pathogen as eradicated.

L. pneumophila:

Review of L. pneumophila infections reveals 40% (4/10) of the patients had another" typical" pathogen isolated in culture. Serologic methodology which was used included PCR, Combined Titer, and Urinary Antigen Testing. None of the PCR tests were positive and only one of the Urinary Antigen tests were positive. Criteria for diagnosis by the applicant per protocol was as follows:

" *Legionella pneumophila* case definition (one or more of the following):

- A single IgG/M/A indirect fluorescent antibody (IFA) titer of ≥1:256 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive urine antigen test;
- A positive oropharyngeal PCR for *Legionella sp.*; and/or
- A positive oropharyngeal culture."

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits that the applicant was using in these studies.

Review of the test kit discription for the combined titer reveals the following:

- "A four-fold rise in titer ≥ 1:128 from the acute to the convalescent phase provides evidence of a recent infection with Legionella. A standing or single titer ≥ 256 provides presumptive evidence of infection at an undetermined time.
- Single titers of less than 256 are not considered evidence of infection."

The criteria the applicant used to evaluate L. pneumophila infection are in agreement with the recommendations in the package insert regarding combined titers.

All but one of the patients designated as having L. pneumophila infections met the serologic criteria for presumed infection (single high titer). One patient had descending titers. None of the patients were designated as having failed.

None of the patients designated as having L. pneumonphila infection had a positive PCR screen. Only one patient had a positive urinary antigen. This patient was listed as being cured and was in the gatifloxacin group.

Overall, the cure rates were similar between treatment groups. Regarding the Bacteriologic response of L. pneumophila, it can only be based upon serologic diagnosis as none of the cases had an culture proven infection. Thus, according to the protocol the patients could be designated as presumptive eradication. It would be inaccurate to describe the pathogen as being eradicated without culture documentation.

Summary of Atypical Pneumonia review:

The overall analysis by the applicant may over-represent the number of cases due to atypical pathogens. While serology may be applied to identify potential cases, additional scrutiny is necessary, given the uncertainty of the interpretation of test results. The FDA 'sanalysis is represented in the table below. Of the cases reported by the applicant, those listed in the table below may represent the cases most likely to have had community acquired pneumonia due to the atypical pathogens listed. The body of evidence required for these pathogens should err on the side of conservatism, especially in the case of L. pneumophila. Legionnaires' Disease has a high mortality rate, and in order to support

the inclusion of this pathogen in the label it is important to include well documented cases.

Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin According to Diagnostic Criteria

	M. pneumoniae	*C. pneumoniae*	*L. pneumophila*
Culture positive (PCR)	*4*	*2*	*0*
Definitive (4X rise in IgG or IgM)	*0*	*1*	*0*
Presumptive (single high titer)	*6*	*4*	*4*
Urinary Antigen	*NA*	*NA*	*1*
TOTAL	*10*	*7*	*5*

** note: test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.*

FDA's analysis reveals that cases of atypical pneumonia on the gatifloxacin treatment arm included 10 cases of M. pneumoniae, 7 cases of C. pneumoniae, and 5 cases of L. pneumophila pneumonia, which were documented according to strict criteria. All of these cases, except one M. pneumoniae, were considered clinical cures. As is noted in the table above, most of these infections were diagnosed upon the basis of a single high titer.

It is difficult to evaluate the true efficacy of gatifloxacin with regard to atypical pneumonia cases that were only documented by serology. M. pneumoniae has a clinical course that is somewhat different that C. pneumoniae and L. pneumophila. It may take a month or two for the symptoms to resolve, even with treatment. A prospective study of each individual disease entity would be most informative with regard to efficacy. Culture is still the gold standard.

Given the data presented by the applicant and the problems inherent in diagnosis by serology, it appears that gatifloxacin is active against these pathogens.

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8.1.3.3 SAFETY RESULTS:

8.1.3.3.1 Overall and Related Adverse Clinical Events:

Overall, gatifloxacin and levofloxacin were well-tolerated. Sixty-five percent of patients experienced one or more adverse events. The most common were experienced by similar numbers of patients and included abnormal breath sounds (11%), nausea (11%) and cough (9%). Headache was encountered more frequently in levofloxacin patients (11% vs. 6% gatifloxacin).

Adverse Clinical Events of All Causes by Relationship to Study Medication, All Treated Patients Protocol A1420-038

	Number of Patients (%)															
	Gatifloxacin N = 209								Levofloxacin N = 208							
Adverse Clinical Event	Related		Unknown Relationship		Not Related		Total		Related		Unknown Relationship		Not Related		Total	
Any Adverse Clinical Event	58	(28)	1	(<1)	74	(35)	133	(64)	67	(32)	2	(<1)	68	(33)	137	(66)
Breath Sounds Abnormal	-		-		23	(11)	23	(11)	-		-		22	(11)	22	(11)
Nausea	13	(6)	-		9	(4)	22	(11)	19	(9)	-		4	(2)	23	(11)
Coughing	1	(<1)	1	(<1)	16	(8)	18	(9)	-		-		20	(10)	20	(10)
Sputum increased	3	(1)	-		15	(7)	18	(9)	-		-		13	(6)	13	(6)
Dyspnea	-		1	(<1)	12	(6)	13	(6)	-		-		10	(5)	10	(5)
Headache	6	(3)	-		6	(3)	12	(6)	6	(3)	1	(<1)	15	(7)	22	(11)
Diarrhea	7	(3)	-		5	(2)	12	(6)	12	(6)	1	(<1)	2	(<1)	15	(7)
Malaise	-		-		10	(5)	10	(5)	1	(<1)	-		10	(5)	11	(5)
Pain Chest	-		-		9	(4)	9	(4)	2	(<1)	-		14	(7)	16	(8)
Insomnia	9	(4)	-		-		9	(4)	9	(4)	-		1	(<1)	10	(5)
Rhinitis	-		-		8	(4)	8	(4)	-		1	(<1)	8	(4)	9	(4)
Vaginitis	8	(4)	-				8	(4)	7	(3)	-		-		7	(3)
Vomiting	2	(<1)	-		6	(3)	8	(4)	4	(2)	-		2	(<1)	6	(3)
Pain Abdomen	6	(3)	-		2	(<1)	8	(4)	2	(<1)	-		2	(<1)	4	(2)
Constipation	2	(<1)	-		4	(2)	6	(3)	6	(3)	-		2	(<1)	8	(4)

Indication: Community Acquired Pneumonia (Study 038)
Revision Date: 22-Nov-99

	Number of Patients (%)															
	Gatifloxacin N = 209							Levofloxacin N = 208								
Adverse Clinical Event	Related		Unknown Relationship		Not Related		Total		Related		Unknown Relationship		Not Related		Total	
Rash	3	(1)	-		3	(1)	6	(3)	-		-		4	(2)	4	(2)
Dyspepsia	3	(1)	-		2	(<1)	5	(2)	6	(3)	-		2	(<1)	8	(4)
Taste Perversion	4	(2)	1	(<1)	-		5	(2)	3	(1)	1	(<1)	-		4	(2)
Pain	1	(<1)	-		3	(1)	4	(2)	1	(<1)	-		11	(5)	12	(6)
Sinusitis	-		-		4	(2)	4	(2)	-		1	(<1)	6	(3)	7	(3)
Dry Mouth	4	(2)	-		-		4	(2)	7	(3)	-		-		7	(3)
Pain Back	-		-		4	(2)	4	(2)	-		-		6	(3)	6	(3)
Disorder Lung	-		-		4	(2)	4	(2)	-		-		5	(2)	5	(2)
Dizziness	3	(1)	-		-		3	(1)	4	(2)	1	(<1)	2	(<1)	7	(3)

a Adverse clinical events occurring in >2% of the total number of treated patients. A patient may have more than one adverse clinical event.
(Reference. Vol 6, p. 118-119)

Fifty-eight (28%) gatifloxacin patients and 67 (32%) levofloxacin patients experienced adverse events that were considered related to study therapy by the Investigator. The intensity of most was mild (55% gatifloxacin/70% levofloxacin) or moderate (36% gatifloxacin/28% levofloxacin). All occurred with similar frequency between treatment groups or slightly more commonly in the levofloxacin group. Nausea was more frequent in levofloxacin patients (9% vs. 6% gatifloxacin), as was diarrhea (6% vs. 3%).

Drug-Related Adverse Clinical Events by Severity of Event, All Treated Patients Protocol A1420-038

	Number of Patients (%)																	
	Gatifloxacin N = 209										Levofloxacin N = 208							
Adverse Clinical Event	Mild		Moderate		Severe		Very Severe	Total		Mild		Moderate		Severe	Not Recorded		Total	
Any Related Adverse Clinical Event	32	(15)	21	(10)	2	(2)	-	58	(28)	47	(23)	19	(9)	-	1	(<1)	67	(32)
Nausea	11	(5)	2	(<1)	-		-	13	(6)	17	(8)	2	(<1)	-	-		19	(9)
Insomnia	7	(3)	1	(<1)	1	(<1)	-	9	(4)	7	(3)	2	(<1)	-	-		9	(4)
Vaginitis	7	(3)	1	(<1)	-		-	8	(4)	5	(2)	2	(<1)	-	-		7	(3)
Diarrhea	3	(1)	4	(2)	-		-	7	(3)	8	(4)	4	(2)	-	-		12	(6)
Headache	3	(1)	3	(1)	-		-	6	(3)	4	(2)	2	(<1)	-	-		6	(3)
Dry Mouth	4	(2)	-		-		-	4	(2)	5	(2)	2	(<1)	-	-		7	(3)
Dyspepsia	2	(<1)	1	(<1)	-		-	3	(1)	2	(<1)	4	(2)	-	-		6	(3)

a Drug-related AEs occurring in >2% of total patients. A patient may have experienced more than one drug-related AE.
(Reference: Vol. 6, p. 121)

Medical Officer Comment:
FDA's review of database provided by the applicant is generally in agreement with the above.

The following adverse clinical events associated with other drugs in the fluoroquinolone class were not commonly seen with gatifloxacin therapy during this study:

Hepatotoxicity: Only three adverse events were reported which related to the liver. Two in the gatifloxacin group and 1 in the levofloxacin group. Of the gatifloxacin patients, one (70-782) was noted to have mild cholecystitis with no liver abnormalities, the other was noted to have an elevation of AST alone with no other symptoms (08-266). The levofloxacin patient was noted to have jaundice (46-562) which was mild and possibly related, according to the investigator. The liver chemistries documented an elevated total bilirubin of 4 mg/dl at baseline and 1 mg/dl at study termination. According to the adverse events reported this is an infrequent event, not directly related to the study drug. (Additional analyses are reported in the laboratory abnormality section below).

Central Nervous System: Insomnia was seen at a comparable rate in each treatment group (11/41 vs 10/41 patients in the gatifloxacin and levofloxacin arms respectively). Vertigo was seen in 5 patients in the gatifloxacin treatment arm and 1 in the levofloxacin arm. In contrast, dizziness was seen more frequently in the levofloxacin group. No seizures were reported in this study.

Tendonopathy: Only one case of tendonitits was reported. This patient was in the gatifloxacin arm (29-0050). This patient had a history of knee surgery and back surgery prior to study entry. It was listed as moderate in severity and unrelated to study drug by the investigator.

Rash: The frequency of rash is similar between the treatment groups occurring in 3% or less of patients treated.

Anaphylaxis: No cases of anaphylaxis were reported.

Cardiac Effects: Arrhythmia was reported in four patients in each study group. One of the patients in the gatifloxacin arm accounted for two of these (atrial fibrillation and bradycardia) diagnosed after an MI and would not be related to study drug (32 209). Another 63 year old male was reported to have tachycardia which was judged as alcohol withdrawal syndrome (70-798). The last patient, a 79 yo male, was reported to have a bradycardia with hypoglycemia (serum glucose 24). He was found by the paramedics and taken to the hospital from which he was discharged. This patient had a history of COPD, CAD and Diabetes mellitus, and was being treated with Glyburide 20 mg per day. He had a history of (07 0013). Overall, these events occurred in a similar frequency to that of the levofloxacin group and most were unrelated to study drug.

8.1.3.3.2 Discontinuation Due to Study Drug:

Ten patients in the gatifloxacin arm and six in the levofloxacin arm discontinued due to an adverse event. Five (50%) of the gatifloxacin patients had discontinuations that were attributed to study medication. Those adverse events included bradycardia, gastrointestinal complaints, dizziness and facial edema; the latter occurred after the first dose. Three of the levofloxacin patients had discontinuations due to adverse events that were attributed to study medication. Those events were asthenia and palpitations, nausea and vomiting, and pruritus. One levofloxacin patient was discontinued for an elevated creatinine level that was obtained pre-treatment.

Discontinuation of Study Medication Due to Adverse Clinical Events or Laboratory Abnormality, All Treated Patients Protocol A1420-038 Treatment Group: Gatifloxacin

Patient Number	Adverse Event or Lab Abnormality	Relationship to Study Drug	Duration of Dosing (Days)	Onset of Event (Study Day)
007-013	Hypoglycemia	probable	2	+1
	Bradycardia	possible	2	+1
013-186	Abdominal cramping	possible	13	L13
022-371	Nausea	possible	2	1
	Tremor	possible		1
	Sweating	possible		1
	Vertigo	possible		1
	Chills	possible		L2
	Hypertension	possible		L2
031-199	facial edema	probable	1	+1
	diarrhea	probable		+1
057-824	Abnormal vision	possible	4	2
	Dizziness	possible		2
	Dyspepsia	possible		3
	chest pain	unlikely		3
034-135	Dyspnea/CHF	unlikely	3	L3
048-234	Vomiting	unlikely	8	L8
048-240	Anorexia	unlikely	9	5
	Dyspnea	unlikely		L9
	Malaise	unlikely		L9
	lung carcinoma	unlikely		+1
070-798	Nausea	unlikely	9	7
	Vomiting	unlikely		7
023-308	Asthma	unlikely	2	+1

(Reference: Vol. 6, p. 124)

Discontinuation of Study Medication Due to Adverse Clinical Events or Laboratory Abnormality, All Treated Patients Protocol AI420-038 Treatment Group: Levofloxacin

Patient Number	Adverse Event or Lab Abnormality	Relationship to Study Drug	Duration of Dosing (Days)	Onset of Event (Study Day)
057-426	Asthenia	possible	8	L8
	Palpitations	possible		
022-372	Pruritus	possible	13	12
008-267	Nausea	possible	12	2
	Vomiting	possible		10
027-036	Abnormal lab (elevated creatinine)	unrelated	2	L2
031-193	heart failure	unlikely	2	+1
	fever	unlikely		+1
038-693	Coughing	unlikely	3	L3
	Malaise	unlikely		L3
	Abdominal pain	unlikely		L3
	chest pain	unlikely		L3

(Reference: Vol. 6, p. 126-127)

The following conventions were used to indicate study periods:
First day of study drug therapy = Day 1;

Days on which study drug was administered = Day 1, Day 2, Day 3, etc.;

Pre-treatment days = Day –2, Day –1, etc.;

Last day of treatment has day number preceded by 'L';

Post-treatment days = Day +1, Day +2, Day +3, etc.

Medical Officer Comment: Review of database and SAS files is in agreement with applicant's analysis. It is interesting to note that the patient described above with bradycardia/hypoglycemia was a diabetic on oral hypoglycemic products. This adverse event(hypoglycemia) was possible exacerbated by the patient's underlying disease and not related to study drug. Hypoglycemia will be discussed in the laboratory abnormalities section below.

8.1.3.3.3 Serious Adverse Events (SAE):

Twice as many gatifloxacin patients (sixteen [8%] gatifloxacin patients and eight (4%) levofloxacin patients) experienced at least one serious adverse event as compared to levofloxacin patients. Two SAEs were considered related to study therapy in the gatifloxacin group, but none in the levofloxacin group. One was bradycardia which occurred in a 79 year old male in association with hypoglycemia on Day 3 (007-013). This patient was discontinued from study therapy. The other SAE was diabetes and occurred in a 79 year old male on Day 11 of study therapy (026-025). The patient was

concomitantly receiving prednisone. The patient completed a 14 day course of therapy, and was started on glyburide. The diabetes resolved after approximately three months.

All other SAEs in both treatment arms were felt to be unrelated to study therapy and could generally be ascribed to patients' underlying disease(s) and/or pneumonia. Four gatifloxacin patients and two levofloxacin patients were discontinued for SAEs, none of which were considered related to study therapy. A number of SAEs led to discontinuation of study therapy, in the gatifloxacin arm these included sepsis and endocarditis (016-570), CHF with associated dyspnea (034-135), vomiting (048-234) and lung carcinoma (048-240). In the levofloxacin arm, SAEs leading to discontinuation included fever and heart failure (031-193) and pneumonia (048-236).

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Serious Adverse Events of All Causes, All Treated Patients
Protocol AI420-038

Adverse Clinical Event	Number of Patients (Number of Total Considered Drug-related) Gatifloxacin N = 209		Levofloxacin N = 208
Any Serious Adverse Clinical Event[a]	16	(2)	8
Fever	-		1
Chest Pain	-		1
Bradycardia	1	(1)	-
Congestive Heart failure	1		1
Endocarditis	1		-
Myocardial Infarction	1		-
Syncope	2		-
Cholecystitis	1		-
Hemorrhage	2		-
Nausea	1		-
Vomiting	2		-
Carcinoma	1		1
Bone Fracture	-		1
Diabetes Mellitus	1	(1)	-
Cerebrovascular Accident	1		-
Pneumonia	-		3
Asthma	1		-
Dyspnea	1		1
Pleural effusion	1		1
Pharyngitis	-		1
Kidney Failure	1		-

[a] A patient may have more than one serious adverse event.
(Reference: Vol. 6, p. 127)

Medical Officer Comment: FDA's review of the data provided is in agreement with the applicant's presentation. Although there were twice as may SAEs in the gatifloxacin treatment group, many of these are probably unrelated to study drug.

Deaths:
One death occurred in the gatifloxacin arm on the fourth day of therapy and was due to hemorrhage from a preexisting oral squamous cell carcinoma. Another gatifloxacin patient expired 31 days after therapy due to a myocardial infarction.

Medical Officer Comment: Neither death reported by the sponsor appears to be related to the study drug.

8.1.3.3.4 Local IV Intolerance:
Although similar numbers of patients received IV study drug, five experienced local intolerance in the levofloxacin arm compared to one in the gatifloxacin arm. The single case of infiltration in the gatifloxacin group occurred at the start of the second dose and was considered mild (049-397). The site was changed and infusion completed uneventfully.

Infiltration in the levofloxacin group occurred during the first dose and a site change allowed for successful infusion for one patient (064-475). Another levofloxacin patient experienced redness extending 4-5 inches above the infusion site during infusion (019-113). The "other" local intolerance was drug leakage into the tissue surrounding the infusion site and resulted in "severe extravasation" (023-309). Burning occurred in two levofloxacin patients; one patient experienced five minutes of burning after every infusion (039-221) and the other had no details provided for their local intolerance (039-220).

Local IV Intolerance, All Treated Patients
Protocol AI420-038

	Number of Patients (%)			
	Gatifloxacin N = 24		Levofloxacin N = 25	
Tolerated Study Drug Well	23	(96)	20	(80)
Local Intolerance	1	(4)	5	(20)
Infiltration	1	(100)	1	(20)
Redness	-		1	(20)
Burning	-		2	(40)
Other	-		1	(20)

(Reference: Vol. 6, p. 128)

Medical Officer Comment: Review of above information reveals minimal iv intolerance with gatifloxacin.

8.1.3.3.5 Laboratory Abnormalities:

Patients with Normal Pre-treatment Values

Few patients with normal baseline laboratory values developed abnormal results during or after treatment. Most that did occur were mild (Grade 1). The most common abnormalities encountered were decreased hemoglobin, elevations in ALT and AST, elevations in BUN, and electrolyte disturbances. Thirteen cases of Grade 2 toxicity occurred in each treatment arm. The distributions of Grade 2 toxicity for individual laboratory tests was similar between treatment arms. There were four instances of Grade 3 toxicity, one in the gatifloxacin arm and three in the levofloxacin arm.

Two patients experienced Grade 4 toxicity, and both were in the levofloxacin arm. One abnormality was an isolated elevation of potassium to 7.4 mEq/L on day seven of therapy, and likely represents a lab error or results from a hemolyzed specimen (060-700). The other grade 4 abnormality involved elevated chloride and began as a Grade 1 abnormality (112 mEq/L) and progressed to Grade 4 on Day 5 (120 mEq/L) (064-475). The day following completion of eight days of therapy, the chloride was 125 mEq/L. No clinical correlates were noted for this elevation.

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Abnormal Laboratory Test Values
Patients with Normal Pre-treatment Values,
All Treated Patients
Protocol A1420-038

	Number of Patients (%)														
	Gatifloxacin N = 209							Levofloxacin N = 208							
Laboratory Test	N[a]	Grade 1		Grade 2		Grade 3		N[a]	Grade 1		Grade 2		Grade 3		Grade 4
Hemoglobin	142	19	(13)	-		-		151	16	(11)	-		-		-
WBC	177	7	(4)	1	(<1)	-		176	4	(2)	-		-		-
Neutrophils	177	10	(6)	2	(1)	-		178	5	(3)	3	(2)	-		-
Platelets	172	7	(4)	-		-		165	2	(1)	-		-		-
Alkaline Phosphatase	167	3	(2)	-		-		163	4	(2)	-		-		-
AST	161	11	(7)	-		-		161	8	(5)	-		-		-
ALT	167	10	(6)	-		-		164	5	(3)	-		-		-
Total Bilirubin	165	-		5	(3)	1	(<1)	154	-		2	(1)	1	(1)	-
BUN/Urea	157	7	(4)	-		-		161	10	(6)	-		-		-
Creatinine	169	3	(2)	-		-		162	4	(2)	1	(<1)	-		-
Glucose Decrease (fasting)	12	-		-		-		8	-		-		-		-
Glucose Increase (fasting)	12	3	(25)	-		-		8	1	(13)	-		-		-
Amylase	168	7	(4)	1	(<1)	-		172	1	(<1)	1	(<1)	-		-
Hyponatremia	163	7	(4)	-		-		159	7	(4)	1	(<1)	-		-
Hypernatremia	163	13	(8)	-		-		159	16	(10)	2	(1)	-		-

Indication: Community Acquired Pneumonia (Study 038)
Revision Date: 22-Nov-99

	Number of Patients (%)													
	Gatifloxacin N = 209						Levofloxacin N = 208							
Laboratory Test	N[a]	Grade 1		Grade 2		Grade 3	N[a]	Grade 1		Grade 2		Grade 3		Grade 4	
Hypokalemia	170	5	(3)	-		-	160	6	(4)	-		-		-	
Hyperkalemia	170	1	(<1)	-		-	160	3	(2)	-		-		1	(<1)
Chloride Decrease	176	1	(<1)	-		-	172	3	(2)	1	(<1)	-		-	
Chloride Increase	176	1	(<1)	-		-	172	7	(4)	2	(1)	1	(<1)	1	(<1)
Hypophosphatemia															
Hyperphosphatemia															
Decreased Bicarbonate	93	23	(25)	3	(3)	-	118	31	(26)	-		1	(<1)	-	
Increased Bicarbonate	93	6	(6)	1	(1)	-	118	1	(<1)	-		-		-	

a For each test, number of patients with a normal pre-treatment value who had at least one during or post-treatment value determined.
(Reference: Vol. 6, p. 130-131)

Worsened Laboratory Test Values, Patients with Abnormal Pre-treatment Values, All Treated Patients Protocol A1420-038

	Number of Patients (%)									
	Gatifloxacin N = 209					Levofloxacin N = 208				
Laboratory Test	Na	Worsened to Grade 2		Worsened to Grade 3		Na	Worsened to Grade 2		Worsened to Grade 3	Worsened to Grade 4
Hemoglobin	37	3	(8)	1	(3)	29	1	(3)	1 (3)	-
WBC	2	-		-		4	1	(25)	-	-
Neutrophils	1	-		-		2	1	(50)	-	-
Platelets	7	-		-		15	-		-	-
Alkaline Phosphatase	11	-		-		13	-		-	-
AST	18	-		-		14	1	(7)	-	-
ALT	12	-		-		12	-		-	-
Total Bilirubin	14	-		-		21	-		-	-
BUN/Urea	22	1	(5)	-		15	1	(7)	-	-
Creatinine	10	1	(10)	-		14	1	(7)	-	-
Glucose Decrease (fasting)	4	-		-		4	-		- 1	-
Glucose Increase (fasting)	4	-		1	(25)	-	-		-	-
Amylase	3	-		-		4	1	(25)	-	-
Hyponatremia	15	-		-		17	-		-	-

Indication: Community Acquired Pneumonia (Study 038)
Revision Date: 22-Nov-99

Laboratory Test	Number of Patients (%) Gatifloxacin N = 209				Levofloxacin N = 208					
	N[a]	Worsened to Grade 2		Worsened to Grade 3	N[a]	Worsened to Grade 2		Worsened to Grade 3	Worsened to Grade 4	
Hypernatremia	15	-		-	17	-		-	-	
Hypokalemia	5	-		-	15	2	(13)	-	-	
Hyperkalemia	5	-		-	15	-		-	-	
Chloride Decrease	2	-		-	4	-		-	-	
Chloride Increase	2	-		-	4	-		-	-	
Hypophosphatemia	-	-		-	-	-		-	-	
Hyperphosphatemia	-	-		-	-	-		-	-	
Decreased Bicarbonate	85	7	(8)	-	58	3	(5)	-	1	(2)
Increased Bicarbonate	85	-		-	58	-		-	-	

[a] For each test, number of patients with an abnormal pre-treatment value who had at least one during or post-treatment value determined.
(Reference: Vol. 6, p. 133-134)

Patients with Abnormal Pre-treatment Values

Few patients experienced worsening of abnormal baseline laboratory values. Twenty-three patients worsened to Grade 2, 12 in the gatifloxacin arm and 11 in the levofloxacin arm. Three patients worsened to Grade 3, two in the gatifloxacin arm and one in the levofloxacin arm. Only one patient, in the levofloxacin arm, worsened to Grade 4. No substantial differences in worsening between treatment arms were noted.

Medical Officer Comment: Overall the laboratory test abnormalities that developed during the study were similar between the two treatment groups. In the patients with normal baseline liver function tests, there were 5 patients in the gatifloxacin group and 4 patients in the levofloxacin group who developed elevated total bilirubin levels. Of the patients in the gatifloxacin arm, the range in elevation was from 1 to 1.3 times the upper limit of normal. Only one of these patients had a concomitant rise in AST/ALT (AST = 1.01xULN). Patients with normal liver functions at baseline also had elevations in ALT/AST without concomitant rise in total bilirubin. Similar numbers were seen in both treatment groups, and were for the most part mild elevations. Only one patient in the levofloxacin group vs. 4 patients in the gatifloxacin group had increases > 2.0 X ULN. Of the four gatifloxacin treated patients most had elevations at under 2.5 X ULN, but only one had a higher grade (4.8-5.1 X ULN). None of these patients were reported to have an adverse outcome, and they appeared to tolerate the complete course of therapy without adverse events.

Of the 63 patients reported in this study to have fasting glucose levels at baseline, none of these patients was reported to have a follow-up glucose value that was in the hypoglycemic range.

8.1.3.3.6 Medical Officer Safety Summary:

The most frequent adverse events were related to the gastrointestinal system, excluding those which may be related to pneumonia. These rates were similar when gatifloxacin was compared to levofloxacin. Dizziness was reported less frequently in the gatifloxacin group than the levofloxacin group. Similar rates of discontinuation due to adverse events were seen in both treatment groups. There were only two deaths in this study, both on the gatifloxacin arm, both unrelated (one death was recorded due to a myocardial infarction 31 days after the treatment had ended). Elevations in liver function tests were noted during study treatment and were mild in nature for the majority of patients, occurring at a similar frequency when both treatment groups are compared. There were 5 patients in the levofloxacin group and 4 patients in the gatifloxacin group who had elevated total bilirubin levels during the study (range < 2.0 X UNL), and only one in each group had a concomitant ALT/AST elevation. The intravenous formulation was tolerated well in both treatment groups, and no major infusion related adverse events were reported.

There were no class related events reported in this study including phototoxicity, tendon rupture, seizures, hypoglycemia, hemolytic uremic syndrome or torsades-de-point.

Gatifloxacin appears to equally well tolerated in compared to levofloxacin in the treatment of Community Acquired Pneumonia.

8.1.3.4 OVERALL CONCLUSIONS:

APPLICANT'S CONCLUSIONS: Gatifloxacin was comparable to levofloxacin for the treatment of patients with CAP caused by common typical and atypical respiratory pathogens. Its antibacterial potency against respiratory tract pathogens, and a favorable safety profile and convenience of once-daily dosing, make gatifloxacin an excellent choice for the treatment of community acquired pneumonia. (date of report: 10-Dec-1998)

MEDICAL OFFICER SUMMARY OF SAFETY AND EFFICACY FOR STUDY 038:

This double-blind, randomized, controlled study demonstrated the efficacy of gatifloxacin, given at a dose of gatifloxacin 400 mg QD (IV to PO or IV only) for 7 to 14 days: to a standard regimen of levofloxacin 500 mg QD (IV to PO or IV only) for 7 to 14 days. The cure rates were somewhat higher for the levofloxacin treated patients in comparison to the gatifloxacin treated patients (93% vs. 90%, respectively in the clinically evaluable patients [95% C.I. –11.5%, 3.6%]).

Applicant Clinical Efficacy Analysis Study 038

Subgroup	Gatifloxacin	Levofloxacin	95% Confidence Interval*
All Treated Patients	83% (173/209)	88% (183/208)	-13.1%, 2.7%
Eligible Patients	89% (168/203)	95% (175/197)	-14.5%, 1.7%
Evaluable Patients	90% (154/172)	93% (166/178)	-11.5%, 3.6%

(Reference. Vol 6) *of the difference in cure rates

The higher cure rate for levofloxacin was stable among the various analysis groups (All Treated Patients, Clinically Eligible. The comparison of gatifloxacin to levofloxacin for the evaluable patient analysis demonstrated a 90% vs. 93% clinical cure rate, respectively. The lower bound of the confidence interval for this comparison (gatifloxacin - levofloxacin) was -11.5%. The applicant had assumed, for purposes of analysis, that the efficacy rates would be in the 80% range when defining the confidence interval for equivalence. In this case, the applicant stated that equivalence would be defined if lower limit of the confidence interval did not exceed -15%. Regarding this bound, where the efficacy rates were in the 90% range, the applicant made no comment. In the past the FDA had recommended the lower bound for the confidence interval of the difference to be no greater than -10%; however, this recommendation is under reconsideration by the FDA. The overall conclusion regarding the comparison of gatifloxacin to levofloxacin shows that the clinical cure rates are lower than those of levofloxacin, and that a weak equivalence relationship was shown in this study. Overall, the lower limits of the confidence intervals did not exceed -15% in these analyses (where the outcomes were in the 80% range or lower), except for the very conservative loss to follow-up analysis. Further, because of the activity to treat pneumonia, this studies are felt to be supportive of the acute exacerbation of chronic bronchitis indication.

A small number of patients were treated with the intravenous preparations (12%). The cure rates in both studies for gatifloxacin in the evaluable patient cohort were similar. Patients considered to have severe pneumonia by the treating physician had a 91% (63/69) cure rate in the gatifloxacin treated patients vs. 90% (53/59) in the levofloxacin treated patients.

With regard to microbiologically documented infections, as would be expected in a pneumonia study, slightly more than half of the patients enrolled did not have a baseline pathogen identified in the sputum. Adequate numbers of *S. pneumoniae, M. catarrhalis, H. influenzae, H. parainfluenzae and S. aureus* were successfully treated in this study, supporting the proposed label. Patients with documented infections due to *K. pneumoniae* were not represented in adequate numbers and will have to be considered in total. across the CAP studies. No patient was documented to have penicillin resistant S. pneumoniae in the baseline sputum. The issue of penicillin-resistance will be considered in the overall summary of CAP, where cases are collected from all five trials submitted in the NDA.

FDA Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin According to Diagnostic Criteria

	M. pneumoniae	*C. pneumoniae*	*L. pneumophila*
Culture positive (PCR)	*4*	*2*	*0*
Definitive (4X rise in IgG or IgM)	*0*	*1*	*0*
Presumptive (single high titer)	*6*	*4*	*4*
Urinary Antigen	*NA*	*NA*	*1*
TOTAL	*10*	*7*	*5*

** note: test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.*

Atypical pneumonia was diagnosed by serology for the most part. When stricter FDA criteria were applied the number of cases treated with each pathogen were lower than that stated by the applicant. *M. pneumoniae* was isolated in culture from 4 patients treated with gatifloxacin, all of whom were considered to be clinical successes. A total of 6 patients in the gatifloxacin group were diagnosed as having *M. pneumoniae* infections (serologically). All of these patients were reported to have been clinical cures except one. Five patients were serologically diagnosed with C. pneumoniae in the gatifloxacin treated arm, and two had positive PCR tests. All of the patients had a good clinical result. Five patients in the gatifloxacin treatment group were identified as being infected with L. pneumonphila, based primarily on serologic diagnosis. Only one had a positive urine antigen and one had a rise in titer. These patients were considered clinical cures. While it is important to document clinical activity to all potential pathogens causing community acquired pneumonia, the diagnosis of atypical pneumonia remains problematic. It should not be stated that there was Microbiologic Eradication of these atypical pathogens, even though the definition in the protocol states that this could be based on clinical cure as a

presumptive eradication. This study supports the inclusion of these pathogens in the label; however, it is highly recommended that a statement be made regarding the low numbers treated and the method of detecting the pathogen (serology).

The safety profile of gatifloxacin was similar to that of levofloxacin at a dose of 500 mg per day. Liver function abnormalities did occur in both treatment groups at a low frequency and to a mild degree, for the most part. No significant clinical effects were a result of these changes. In addition, these changes may be, in part, due to the underlying pneumonia. The intravenous formulation appears to be well tolerated in comparison to the levofloxacin group, with no major infusion site problems. No quinolone class adverse events were reported in this study; seizures, phototoxicity, tendon rupture, HUS or torsades de pointe. Hypoglycemia was reported in the gatifloxacin group; however, it may have been related to the patient's diabetic status.

APPENDIX A

Atypical Pathogen Serologic Data

* indicates culture positive cases of *M. pneumoniae*

Where serologic results are unchanged from the pre- value, only one value is listed. Where a pre- or post- test was not performed it is listed as ND.

3 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

8.1.4 STUDY # AI420-003: An Open-Label Multicenter Non-Comparative Phase II/III Study of Oral Gatifloxacin in the Treatment of Community-Acquired Bacterial Pneumonia.

8.1.4.1 STUDY DESIGN:

OBJECTIVES: 1) To establish the clinical and bacteriologic efficacy of gatifloxacin at a dose of 400 mg QD in the treatment of acute community-acquired bacterial pneumonia; 2) To evaluate the safety profile of gatifloxacin at 400 mg QD in this patient population.

METHODOLOGY: This was an open-label, non-comparative multicenter study.

Medical Officer Comment: This study is considered supportive because of its open-label design, and will contribute additional microbiologically evaluable patients with culture proven infections.

CLINICAL PHASE: II/III.
STUDY PERIOD: 18 Feb 1997 to 17 Apr 1998
INVESTIGATORS: Multiple (28).
PUBLICATIONS: None.

STUDY CENTERS: 10 centers in the U.S.; 3 centers in Australia; 5 centers in S. Africa; 5 centers in Argentina; 2 centers in Brazil; 1 center in Canada and 2 centers in Mexico. Fifty-one patients were enrolled in North America (US and Canada) and 100 patients in all the other countries. Argentina enrolled 40% of the patients. Of the 45 sites selected, seventeen sites did not enroll any patients

Medical Officer Comment: The majority of patients were enrolled from other countries (100 patients) and 51 were enrolled in North American Countries. This strategy was aimed at acquiring patients with documented penicillin resistant S. pneumoniae.

PROTOCOL AMENDMENTS:
There were 3 amendments to the protocol. The first amendment dated January 31, 1997, (prior to enrollment of the first patient) provided for the following changes:

- Elimination of the requirement of fever for inclusion to the study;
- Dosing instructions were modified to minimize the potential effect that concomitant food intake might have on gatifloxacin absorption;
- Elimination of the withdrawal from the study due to drug-related adverse events as a reason for Clinical Failure;
- Clarify the assessment of response for patients with resistant pre-treatment pathogens;
- Added a Clinical Response category of Relapse;
- Clarify pre-treatment and post-treatment procedures;
- Addition of a positive pregnancy test as a reason for study discontinuation;
- Eliminate the collection of subculture, sputum assessment and chest x-ray at the extended follow-up visit.

The second amendment dated February 4, 1997 provided for the optional collection of blood samples during dosing with gatifloxacin in order to evaluate the pharmacokinetic

variables of peak plasma concentration and area under the curve in relationship to specific pharmacodynamic variables such as clinical response or microbiologic outcome. The results of this data collection are discussed in a separate report.

The third amendment dated September 15, 1997 applied only to study sites in Brazil and excluded all women who were not post-menopausal for at least 12 months or who were not surgically sterilized. This change was initiated following a directive from the Ministry of Health in Brazil.

Numerous Administrative Letters were submitted, mostly providing for the name of the medical monitor to be contacted in the case of serious adverse events. The last Administrative Letter (dated September 17, 1997) submitted to all study sites in all countries provided for updated definitions of the Clinical Responses of CURED and FAILURE.

Medical Officer Comment: These amendments were submitted to the IND and reviewed by the FDA.

8.1.4.1.1 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Male or female outpatients, 18 years or older, in whom a medical history, physical examination, and laboratory/radiologic findings were the foundation of a clinical diagnosis of acute, community-acquired pneumonia due to a bacterial organism. The minimum criteria required to meet this diagnosis were:

- presence of a new infiltrate(s) on chest x-ray;
- production of purulent sputum, as defined microscopically by >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field;
- Clinical evidence of acute bacterial pneumonia demonstrated by:
- presence of a new infiltrate(s) on chest x-ray;
- fever (documented temperature >38 C) [>100.4 F];
- production of purulent sputum, as defined by >25 polymorphonuclear leukocytes (PMN) and <10 squamous epithelial cells per low-power field;
- PLUS two or more of the following:
  - chest pain,
  - findings on auscultation or chest percussion consistent with consolidation (e.g., breath sounds, egophony, etc.),
  - cough,
  - leukocytosis (>10,000 WBC/uL or >15% band forms),
  - chills,
  - chest retractions.

Medical Officer Comment: Clinical resolution was based on those signs and symptoms listed above. Additional symptoms were collected; however, those listed above were considered to constitute the clinical definition for atypical pneumonia.

8.1.4.1.2 NUMBER OF PATIENTS: The target enrollment was 200 patients. The study was closed early due to poor enrollment.

Demographics: More then half of the patients were male; the majority were white. The median age was 43 years.

Most of the patients were less than 66 years of age and had no history of comorbid disease or episode of pneumonia within the past year. Six patients (13%) had comorbid disease including four with COPD either alone or in combination with congestive heart failure or diabetes mellitus; the remaining two patients had either congestive heart failure or diabetes mellitus. Five patients had multilobar pneumonia and additional four had interstitial pneumonia. The five cases of multilobar pneumonia met the criteria defining severe, all other cases were considered mild or moderate.

8.1.4.1.3 DISTRIBUTION OF PATIENTS:

A total of 151 patients were enrolled. One patient was not treated and therefore not included in any analysis. This patient, 040-004, provided written informed consent and then decided not to take the study medication.

All Treated Patients: 150 (69 male, 81 female; 18 – 92 years old).
Clinically Eligible Patients: 134 (63 male, 71 female; 18 – 92 years old.
Clinically Evaluable Patients: 122 (58 male, 64 female; 18 – 92 years old).

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Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients
Protocol AI420-003

	Number (%) of Patients	
Study Population/Reason Excluded	N = 150	
Eligible	134	(89)
Ineligible	16	(11)
Reason Ineligible:		
Absence of evidence of pneumonia on pre-treatment chest x-ray	6	(4)
Less than required pre-treatment signs/symptoms	4	(3)
Absence of sputum purulence	4	(3)
Pre-treatment procedures outside window	2	(1)
Clinically Evaluable	122	(81)
Clinically Unevaluable	28	(19)
Reason Unevaluable:		
Ineligible	16	(11)
Did not receive 5 days of study drug therapy due to adverse event	3	(2)
No follow-up chest x-ray performed	3	(2)
Lost to follow-up (No Test of Cure Visit)	2	(1)
Test of Cure Visit outside window	2	(1)
Adverse event before assessment possible	2	(1)
Microbiologically Evaluable[a]	69	(46)
Microbiologically Unevaluable	81	(54)
Reasons Unevaluable:		
No pre-treatment pathogen	66	(44)
Pathogen present but clinically unevaluable	14	(9)
No pre-treatment culture performed	1	(<1)

a One patient was diagnosed serologically with Chlamydia.
(Reference: Vol. 8, p. 59)

Medical Officer Comment: SAS data sets and CRFs were reviewed by the FDA and applicant's above assignments are acceptable. Again it is important to note that more than half of the patients had no pathogen isolated from sputum cultures.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: 400 mg gatifloxacin film-coated tablets (Lot No. N97004 and Lot No. N97070) taken orally (PO) once a day (QD).

8.1.4.1.4 DURATION OF TREATMENT: Gatifloxacin, QD x 14 days. One hundred twenty-eight (85%) of the patients received 14 doses of gatifloxacin. Five patients completed 14 doses over 15 days and one patient over 16 days. Three patients experienced a delay in dosing due to adverse events and three patients forgot to take study medication one day. The majority of the patients (84%) received 14 doses over 14 days. Three of the eight patients who received from 1 to 4 days of gatifloxacin were discontinued due to adverse events and three patients were early treatment failures. One patient was withdrawn by the Investigator due to a normal baseline chest x-ray and one patient withdrew consent. Two patients, 009-006 and 009-007, were lost to follow-up, therefore, dosage duration is unknown.

8.1.4.1.5 CRITERIA FOR EVALUATION: Clinical and bacteriologic responses were determined between 7 and 14 days after the end of study drug therapy (i.e., Test of Cure Visit).

A medical history, complete physical examination including chest x-ray, vital signs, clinical evaluation of the signs and symptoms, chest x-ray, and various cultures and specimens were obtained within 48 hours prior to the start of gatifloxacin treatment. Evaluation of the patient's clinical and safety status was made between Days 3 and 5 of study drug therapy. Between 1 and 3 days after the end of treatment, a follow-up telephone contact was made; if the patient's signs and symptoms had not resolved at this time, an immediate office visit was scheduled in which the post-treatment procedures were performed. For all other patients, the post-treatment visit (i.e., Test of Cure Visit) was scheduled between Days 7 and 14 after the end of study drug therapy in which the patient was evaluated as thoroughly as was done at the pre-treatment visit. In addition, there was an extended telephone contact follow-up visit between Days 21 and 28 to evaluate the occurrence of relapses, new infections and adverse events.

8.1.4.1.6 OUTCOME ANALYSIS

Efficacy Analysis: All patients whose signs and symptoms of pneumonia had resolved or improved without the need for further antimicrobial therapy and chest x-ray abnormalities had either improved or not progressed were assigned a clinical response of cured. A clinical response of failure indicated no clinical or radiographic response of the original infection to treatment with study drug.

Microbiologic Response: A bacteriologic response of eradicate was assigned when the original pathogen was absent from a good quality sputum specimen. If the patient was not producing sputum and the clinical response was cured, the bacteriologic response was considered presumed eradicated. Other bacteriologic responses were documented persisted: continued presence of pathogen in culture and presumed persisted: patient was a clinical failure but not producing sputum. Any patient who was cured at the Test of

Cure Visit but in whom signs and symptoms of the original infection recurred during follow-up was considered a relapse.

New infections were those in which a new pathogen was isolated or signs and symptoms were indicative of a new infection but no culture was obtained at another site (e.g., urinary tract).

Safety: Data included for safety evaluation were: clinical signs and symptoms, physical examinations, vital sign measurements, clinical laboratory test results, and adverse events. Follow-up information was obtained regarding the course of any pregnancy, including perinatal and neonatal outcome, that occurred within at least 6 half-lives after study drug treatment was stopped.

8.1.4.1.7 **STATISTICAL METHODS:** There were four study populations of interest:

All Treated Patients: All patients known to have received at least one dose of gatifloxacin.
Clinically Eligible Patients: All treated patients with a diagnosis of community-acquired pneumonia at entry as defined by the presence of a new infiltrate(s) on pre-treatment chest x-ray and the production of purulent sputum defined by >25 PMNs and <10 epithelial cells per low-power field or the isolation of a respiratory pathogen from at least one pre-treatment blood culture. The patient must have also demonstrated two or more signs or symptoms of bacterial pneumonia at study entry such as chest pain, cough, chills, chest retractions, leukocytosis (>10,000 WBC/uL or 15% band forms) or findings on auscultation/chest percussion consistent with consolidation.
Clinically Evaluable Patients: All eligible patients who had a duration of dosing of at least 5 days (at least 3 days for treatment failures) and received at least 80% of the planned doses; a post treatment clinical assessment within the Day +5 to Day +28 window; a chest x-ray at the Test of Cure Visit; and did not receive any presumably effective systemic antibacterials between the time of the pre-treatment visit and the post-treatment assessment.
Microbiologically Evaluable Patients: All clinically evaluable patients who had at least one gatifloxacin-susceptible pathogen isolated from a good quality sputum or blood culture; and had a culture performed on a purulent sputum specimen produced at the test-of-cure visit (within the Day +5 to Day +28 window).

Medical Officer Comment: Because of the similarity in analysis and evaluation of this study to the previously described comparative trials, this reviewer will not repeat comments already made in the previous reviews.

APPEARS THIS WAY
ON ORIGINAL

8.1.4.2 EFFICACY RESULTS:

8.1.4.2.1 Clinical Efficacy – Eighty-nine percent of Clinically Evaluable Patients were assessed as cures (95% CI: 82.5, 94.2). All patients with bacteremia were cures.

Clinical Response at Test of Cure Visit,
Clinically Evaluable Patients
Protocol AI420-003

Clinical Response	Number (%) of Patients N = 122		95% Confidence Interval
Cured	109	(89)	(82.5%, 94.2%)
Failure	13	(11)	

(Reference: Vol. 8, p. 80)

Failures were analyzed by symptoms, radiographic changes, time to failure, and subsequent therapy. Failure rates by sites were also reviewed. Ten patients failed due to worsening or persistence of their initial signs/symptoms of pneumonia. The remaining three patients had a progression of radiographic abnormalities despite resolution of signs/symptoms.

Four of the thirteen failures occurred during therapy; two at Day 3, one at Day 4, and another at Day 9. The other nine patients were determined to be failures anywhere from the last day of study therapy to Day +14.

Five of the thirteen patients (38%) that failed had partial resolution of signs and symptoms and did not receive any further antibiotic treatment for pneumonia, 007-004, 009-004, 032-002, 032-019 and 041-001. Of these five, two patients, 009-004 and 041-001, had *S. pneumoniae* isolated pre-treatment, the other three, 007-004, 032-002 and 032-019, did not have a pre-treatment pathogen isolated.

One third (4/13) of the failures were from site –009. This site enrolled 10/150 (7%) of the evaluable patients. This included two of the six *S. pneumoniae* failures. One of these, patient, 009-004, had clinical resolution of dyspnea, chills and chest pain with improvement in cough and sputum production as well as eradication of *S. pneumoniae* from a qualifying sputum; but a new infiltrate was present on the Day +6 chest x-ray. The other *S. pneumoniae* patient, 009-003, from this site had near resolution of his chest x-ray when performed on Day +1, however, chills, cough, dyspnea and sputum production remained unchanged. The investigator speculated that his symptoms may have been related to cocaine use.

There were seven discrepancies between the Investigator's assignments of clinical response and those of the applicant medical monitor upon review of the data. Three patients were assigned a clinical response of Cured by the Medical Monitor, whereas the Investigators had assigned them a response of Failure. Two patients were assigned a response of Cured by the Investigator, whereas the Medical Monitor assigned a response of Unable to Determine and Failure. The remaining two patients were assigned a

response of Unable to Determine by the Investigator of which the Medical Monitor assigned one a response of Cured and the other a response of Failure.

Medical Reviewer Comment: Review of SAS data files, CRFs and study report is in agreement with the applicant's assignments.

The only prognostic indicators with a lower response rate were History of Comorbid Disease (79% cure with vs. 94% cure without) and patient age (>65 years 82% cure vs. ≤65 years 92% cure).

Medical Officer Comment: One would expect a lower response rate in these at risk categories. These rates are similar to those in the controlled clinical trials for these subgroups (especially the all treated analysis and study #037, which enrolled sicker patients).

8.1.4.2.2 MICROBIOLOGICAL EFFICACY:

Microbiologic Responses:

The clinical cure rate among evaluable patients with a respiratory pathogen, was 66/77 (86%), and 46/51 (90%) in patients with normal flora. Gatifloxacin was effective in patients infected with all three of the principal respiratory pathogens: in 94% (31/33) of patients with *H. influenzae*, in 79% (22/28) of the patients with *S. pneumoniae*, and in 82% (9/11) of the patients with *M. catarrhalis*.

Of the twenty-eight patients with *S. pneumoniae* isolated in sputum, six patients (21%) were treatment failures. Patients with this pathogen that failed had risk factors for severe disease. Four of these patients had a history of comorbid disease and two of these patients were >65 years of age, one patient, 003-005, had three prognostic factors.

The *S. pneumoniae* failures were frequently technical in nature, four of the six were determined to be failures after completion of therapy. Three of these, 003-005, 009-004, and 030-001, failed due to progression of radiographic abnormalities. These patients had factors that may cause slow radiographic resolution. Patient 003-005, was 73 years old and had multilobar involvement. Patient 030-001, was also elderly. One of the failures, 003-005, had a persistent *S. pneumoniae* recovered from the sputum at Day +8, his symptoms had resolved or improved but radiograph had an infiltrate worse than baseline. Four of the six failures were treated with additional antibiotics.

One patient, 052-001, diagnosed serologically with Chlamydia pneumonia was considered cured.

Clinical Cure Rate by Pathogen, Microbiologically Evaluable Patients Protocol AI420-003

Pathogen[a] /Subtype	Number Cured/ Number Isolated (%)	
SPUTUM:		
Normal flora	46/51	(90)
All pathogens:	66/77	(86)
H. influenzae	31/33	(94)
β-Lactamase -	26/27	(96)
β-Lactamase +	5/5	(100)
β-Lactamase Unknown	0/1	
S. pneumoniae	22/28	(79)
Penicillin Susceptible	12/15	(80)
Penicillin Intermediate	5/6	(83)
Penicillin Sensitivity Unknown	5/7	(71)
M. catarrhalis	9/11	(82)
β-Lactamase -	2/2	(100)
β-Lactamase +	7/9	(78)
Other Gram-positive[b]	3/4	(75)
Other Gram-negative[c]	1/1	(100)
BLOOD:		
All pathogens:	5/7	(71)
S. pneumoniae	4/6	(67)
Penicillin Susceptible	3/3	(100)
Penicillin Intermediate	1/2	(50)
Penicillin Sensitivity Unknown	0/1	
H. influenzae	1/1	(100)
β-Lactamase -	1/1	(100)

a Patients may be included in more than one category.
b *S. pyogenes* x2, *S. aureus* x2.
c *P. aeruginosa.*

(Reference: Vol 8, p. 87)

Medical Officer Comment: This study did not include patients with S. pneumoniae which were resistant to penicillin. In general, response rates were comparable to those of the randomized CAP studies.

8.1.4.2.2.1 NEW INFECTIONS:

Nine of the All Treated Patients experienced a new infection. Of these patients, seven had new respiratory infections. The respiratory tract infections consisted of four upper respiratory tract infections (two unspecified, one viral and one sinusitis), two bronchitis and one pneumonia. Only the sinusitis and pneumonia were treated with antibiotics. Patient, 009-011 was felt to have a new pneumonia based on the development of cough, chills, anorexia, nausea and malaise with *S. pneumoniae* (penicillin-sensitive) isolated eight days after the completion of therapy. This patient had had *H. influenzae* isolated at baseline. The follow-up chest x-ray taken at the time of the isolation of this new organism was essentially unremarkable revealing clearing of the infiltrate noted at baseline. The patient was treated with clarithromycin for seven days. Patient, 053-006, was enrolled in the protocol with consolidation of the right lower lobe. After initial improvement, his symptoms worsened resulting in hospitalization. A right main bronchial biopsy demonstrated poorly differentiated squamous carcinoma. Bronchial washing obtained at this time grew *serratia marcescens*, susceptibility to gatifloxacin was not performed. Gatifloxacin was discontinued and Augmentin and [redacted] therapy were initiated. Patients 032-002 and 032-019 developed bronchitis (no culture done) fourteen and twenty-four days, respectfully, after the completion of study medication. Neither patient was treated with any antibiotic since both infections were thought to be viral in nature. Normal flora had been isolated pre-treatment.

Two patients developed vaginitis and received antifungal therapy. An additional six patients were diagnosed with vaginitis that were not considered new infections since they were not treated with antifungal therapy. All but one case of vaginitis, 053-005, resolved between three to twelve days. This patient, 053-005, was not treated with antifungal therapy, was listed as having continued symptoms at the last follow-up visit.

New Infections, All Treated Patients
Protocol AI420-006

Infection Type/Diagnosis	Number (%) of Patients N = 45
Number of Patients Reporting Any New Infection[a]	9 (20)
Bronchitis	3 (7)
Upper Respiratory Infection	2 (4)
Colitis	1 (2)
Influenza	1 (2)
Pneumonia	1 (2)
Sinusitis	1 (2)
Streptococcal Pharyngitis	1 (4)

[a] Patients may have more than one new infection.
(Reference: Vol 8. , p. 76)